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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,604	02/27/2004	Ralph M. Ellison	2302H	9050
27573	7590	12/01/2006	EXAMINER	
CEPHALON, INC. 41 MOORES ROAD PO BOX 4011 FRAZER, PA 19355			PAK, JOHN D	
			ART UNIT	PAPER NUMBER
			1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/789,604

Applicant(s)

ELLISON ET AL.

Examiner

JOHN PAK

Art Unit

1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 September 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 3-12 and 16-18 are is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) _____ is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Claims 1, 3-12 and 16-18 are pending in this application.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3-12 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over CN 1079391 in view of Zhang (US 6,720,011), Shimotsuura et al. and Smith for the reasons of record.

CN 1079391 discloses the use of highly pure trivalent arsenic oxide in combination with traditional Chinese medicine to treat cancer (English translation of claim 1 & translation page 7, first full paragraph). Treatment of body cavity tumors with arsenic trioxide is taught (translation page 7, first full paragraph). Treatment of skin cancer with white arsenic paste or arsenic trioxide is already known (Translation page 6, lines 13-20). Paste and injection formulation of arsenic trioxide for body surface tumors are taught (paragraph bridging pages 7-8 of the translation; see also translation page 12, last paragraph).

Zhang discloses treating various cancers with arsenic trioxide. See column 1, lines 4-6, 33-35 and 41-43. Cancer of the liver is disclosed (column 1, line 35). Intravenous composition containing 1-10 g arsenic trioxide, sodium chloride and water (column 1, lines 41-54). "[S]trong abruptive effect on the membranes of cancer cells" is

disclosed, as well as inhibition of DNA/RNA synthesis (column 1, lines 58-61). Effective daily dose for an adult is disclosed as 10 ml of the composition containing 10 g/l arsenic trioxide added to 500 ml of 10% glucose solution is disclosed. This calculates to about 67 mg/day. Appropriate dose is to be "decreased accordingly for children" (column 2, lines 9-16).

Shimotsuura et al. disclose that antineoplastic actions of arsenic trioxide are primarily achieved by DNA composition blockage (page 25 of the English translation, top of page 49 in the original).

Smith discloses that radiation to soft tissue lining body cavities is known to be useful in the treatment of cancers such as cancer of the bladder, colon, urethra (column 1, lines 18-21).

CN 1079391 does not **explicitly** disclose treating cancer (i.e. elected subject matter cancers) in a human by administering a combination of arsenic compound and radiation, either alone or in combination with a additional chemotherapeutic or radiotherapeutic agents. However, for the reasons to follow, the claimed invention as a whole would nonetheless have been obvious to the ordinary skilled artisan in this field at the time the invention was made.

CN 1079391 teaches efficacy of arsenic against body cavity tumors. Although elected cancer types are not expressly disclosed in verbatim language, it would have been obvious from the disclosure of CN 1079391 that cancers such as bladder cancer (a body cavity cancer) and related cancer such as cervical cancer (another body cavity

cancer) are clearly suggested from said disclosure. Body cavities are lined with epithelial cells and said cells make up the cells in ovarian, bladder and prostate cancers. Further, Zhang broadly teaches efficacy of arsenic trioxide against cancers, including liver cancer, and a strong abruptive effect on the membranes of cancer cells and inhibition of DNA/RNA synthesis. Taken with teachings of Shimotsuura et al., which confirm the DNA composition blockage action of arsenic trioxide antineoplastic, the ordinary skilled artisan in this field would have been motivated to administer arsenic trioxide to treat patients with the cancers included in the elected subject matter, as claimed. Because those cancers involve uncontrolled growth of cells, one having ordinary skill in the art would have been motivated to administer arsenic trioxide to treat such uncontrolled growth of cells, particularly in view of its adverse effect on rapid DNA replication. The ordinary skilled artisan would have been motivated to further utilize another anti-cancer treatment such as radiation to obtain additional treatment. Smith provides this motivation because Smith establishes that cancers of the type claimed by applicant are already known to be treated with radiation.

Applicant's dependent claim feature of ionic aqueous solution is noted. Ionic aqueous solution is suggested by the various ions in CN 1079391 (translation of claim 5) and the sodium chloride present in Zhang's arsenic trioxide solution (column 1, lines 44-45).

Varying the dose according to the body weight of a human (applicant's claim 11) is suggested by Zhang's teaching of appropriately decreasing the dose for children.

IV administration is suggested by the injection formulation of CN 1079391 and explicit IV injection teaching of Zhang.

As for combined use with radiation or other chemotherapeutic agents, such method would have been fairly suggested from the conventional practice in the cancer treatment field to combine the actions and benefits of several therapies to attack the cancer cells from a variety of mechanisms. The therapeutic agents listed in claim 10 are all well-known anti-cancer agents and inclusion of such additional anti-cancer agents in combination with arsenic trioxide would have been fairly suggested.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly suggested by the teachings of the cited references.

Applicant's arguments relative hereto, filed on 9/15/2006, have been given due consideration but they were deemed unpersuasive.

Applicant argues that "those skilled in the art would not have reasonably expected at the time of the invention that a combination of arsenic trioxide and radiation could have been successfully used to treat colon, ovarian, renal, bladder or prostate cancer in humans." Applicant criticizes each of the cited prior art references for supposed deficiencies, e.g. teachings of the prior art are not predictive of efficacy against other types of cancers such as colon, ovarian, renal, bladder and prostate cancers. The Examiner cannot agree for the reasons set forth below.

Applicant notes that the CN 1079391 patent states “they are still unable to touch upon in vivo cancer tumors,” but the quoted part there relates to a prior art survey, not the invention of CN 1079391. The invention of CN 1079391 is an improvement over the prior art in using higher purity trivalent arsenic oxide compound to treat “body surface and cavity tumors into the body” (translation page 7, first full paragraph, lines 5-7). “[D]irect injection against in vivo cancer entities” is expressly disclosed for body cavity tumors (translation page 8, lines 4-5).

Applicant characterizes the teachings of CN 1079391 as unwarranted generalizations and cites an article from *Medical Oncology* to argue against broad efficacy against numerous cancer types. The Examiner cannot agree. It is applicant who is mischaracterizing the prior art as a whole.

CN 1079391 discloses 16 cases of effective skin cancer treatment with arsenic trioxide¹, 188 cases of effective cervical cancer treatment with white arsenic, i.e. arsenic trioxide². CN 1079391 then teaches treatment of “in vivo cancer entities” of body cavity cancers³ (emphases added). Note that body cavities are lined with epithelial cells and said cells make up the cells in ovarian, bladder and prostate cancers.

Added to these teachings, a valid U.S. Patent by Zhang claims efficacy of arsenic trioxide against leukemia (claims 1-4) and discloses efficacy against cancers in general and hepatoma and lymphoma in particular (column 1, lines 33-35). Moreover, Zhang

¹ Translation page 6, lines 17-20.

² Translation page 6, line 21 to translation page 7, line 3.

³ Translation page 7, first full paragraph; paragraph bridging translation pages 7-8.

teaches that the arsenic trioxide containing composition “exert a strong abruptive effect on the membranes of cancer cells, such as leukemic cells” and inhibits DNA/RNA synthesis (emphases added). Note, Zhang does not limit this teaching to only leukemic cells, as applicant erroneously asserts.

Finally, Shimotsuura et al. disclose that antineoplastic actions of arsenic trioxide are primarily achieved by DNA composition blockage, thereby confirming Zhang’s teachings (page 25 of the English translation, top of page 49 in the original). Applicant argues that Shimotsuura’s teaching is limited to the tested Sarcoma-180 cell line (soft tissue cancer cells), but the ordinary skilled artisan in this field would not understand the prior art that narrowly. Given the summary of prior art knowledge regarding anticancer activity of arsenic and arsenic trioxide as set forth above, Shimotsuura’s disclosure would not be viewed as being limited to sarcoma cancers. The cell line used by Shimotsuura is a commonly used tumor model, and Zhang already confirms that the DNA composition blockage mechanism is present in other cancer cells.

In sum, the prior art teaches that arsenic trioxide is effective against many different types of cancers: (1) skin; (2) cervical; (3) in vivo body cavity cancer entities, which have the same epithelial cells as colon, ovarian, renal bladder, prostate cancers; (4) leukemia; (5) hepatoma; (6) lymphoma. Moreover, arsenic trioxide exerts an inhibition of DNA synthesis, which mechanism is reported by two researchers and with respect to at least two different types of cancers. This is a complete rebuttal of applicant’s expectation of success and “not predictive” arguments and reliance on the

article from *Medical Oncology*, because arsenic trioxide has actually been taught to be effective against many different types of cancers. Because (1) epithelial cells make up the cells in colon, ovarian, bladder and prostate cancers and the disclosed "body cavity" cancers such as cervical cancer are also made up of the same epithelial cells, and (2) the many different types of cancers against which arsenic trioxide is effective against involve uncontrolled growth of cells, one having ordinary skill in the art would have been motivated to administer arsenic trioxide to treat the claimed cancers and their uncontrolled growth of cells, particularly in view of its adverse effect on rapid DNA replication. The ordinary skilled artisan would have been motivated to further utilize another anti-cancer treatment such as radiation to obtain additional treatment. Smith provides this motivation because Smith establishes that cancers of the type claimed by applicant are already known to be treated with radiation.

For these reasons, all claims must be rejected again.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.


Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620**. The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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